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PDE-5 Inhibitors and the Increase Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Males with Erectile Dysfunction

Shayne Ahwah

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Abstract

Background: PDE-5 inhibitors are effective treatments for erectile dysfunction and are one of the best selling drugs. Like most drugs they have side effects, and permanent vision loss due to nonarteritic anterior ischemic optic neuropathy (NAION) has been reported with the ingestion of these medications. Several case reports have shown a correlation between the two, but with lack of clinical trials there is no clear evidence of its existence. Can PDE-5 inhibitors increase the risk of developing NAION in males with erectile dysfunction?

Methods: An exhaustive literature search using MEDLINE-Ovid, MEDLINE-PubMed, Web of Science, ClinicalKey, and CINAHL was performed using keywords: PDE-5 inhibitors, ischemic optic neuropathy, and NAION. These were screened with eligibility criteria. The resulting study and case reviews were then appraised and assessed for quality with GRADE.

Results: One observational study and two case reviews were included in this systematic review. The observational study looked at 40 cases with intermittent PDE-5 inhibitor exposure in the 30 days prior to NAION onset. This study showed a twofold-increased risk of acute NAION within 5 half-lives of PDE-5 inhibitor use. The case reviews revealed the same results, but with co-morbidities.

Conclusion: PDE-5 inhibitors have been successful in providing relief to patients who suffer from erectile dysfunction; however, the permanent loss of vision is alarming, and needs to be further investigated. Additional research into the effects of this medication is essential to healthcare providers when they decide to prescribe this drug.

Keywords: PDE-5 inhibitor, NAION, and ischemic optic neuropathy.

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Biography

Shayne Ahwah was born in Kailua, Hawaii and did her undergraduate degree at the University of Nevada, Reno. She double majored in Biochemistry and Neuroscience. After completion of her degree, she worked in a Neuro-Ophthalmology Clinic as a technician for 5 years, to gain more medical experience. The experience at the clinic influenced the idea for the topic of this paper, and she hopes to practice as a Physician Assistant in Neurology or Emergency Medicine.

Acknowledgements

To *my family and friends*: Thank you for helping me to succeed and for supporting me through this journey. The best is yet to come!

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List of Abbreviations

ED	Erectile Dysfunction
HTN	Hypertension
NAION	Nonarteritic Anterior Ischemic Optic Neuropathy
OR	Odds Ratio
RAS	Renin-Angiotensin System

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BACKGROUND

Erectile dysfunction (ED) is a disorder that occurs during sexual stimulation that prevents the formation of an erection. Pharmaceutical companies developed a drug class, known as PDE-5 inhibitors, to aid in this issue. PDE-5 inhibitors release nitric oxide in the corpora cavernosa during sexual stimulation, which causes smooth muscle relaxation, vasodilation, and increased blood flow into the spongy tissue of the penis, thereby resulting in an erection.[1] Every medication has side effects though, and this medication has a history of causing painless yet permanent visual symptoms. These side effects are involved in the activation and modulation of the phototransduction cascade in retinal cone and rod cells.[2] Since the introduction of this medication 10 years ago, there have been a number of reports of patients developing acute monocular visual loss due to nonarteritic anterior ischemic optic neuropathy (NAION) within hours of ingesting a PDE-5 inhibitor.[3] Subsequently, the vision loss and color perception changes are permanent and develop into a rare disorder of NAION.

NAION is a monocular defect and is caused by rapid ischemia to the optic nerve. It is related to the compromised circulation through the short posterior ciliary arteries due to episodes of hypotension and underlying vascular disease.[4] The lack of oxygen causes acute vision loss, that progresses over time, leading to permanent optic nerve destruction. This destruction is troubling and several case reports have shown a correlation between PDE-5 inhibitor use and NAION. Although, there is some research on this topic, it is of low quality and, further research should be done to answer the question; can PDE-5 inhibitors increase the risk of developing NAION in males with erectile dysfunction?

METHODS

An exhaustive literature search using MEDLINE-Ovid, MEDLINE-PubMed, CINAHL, ClinicalKey, and Web of Science was conducted. The following search words were used: "PDE-5 inhibitors," "ischemic optic neuropathy," and "NAION." Several background articles were used and eligibility criteria were applied to compile this paper. Included were studies that evaluated the correlation between males with erectile dysfunction who used PDE-5 inhibitors and the onset of NAION. Studies were excluded if they were not human trials or were not published in the English language.

RESULTS

The initial research yielded 25 articles to review however, after screening these results and using the eligibility criteria, there were only one observational study[5] and two case review articles[6, 7] reviewed (see Table 1).

Campbell et al

This was the observational study[1] performed in 2015 and was a blind review of records from102 ophthalmology centers in the United States and Europe. The authors wanted to look at each NAION case's PDE-5 inhibitor exposure immediately prior to the onset of vision loss. They used a case-crossover design in which each case subject serves as his own control. This study was well designed to address whether the use of PDE-5 inhibitors is associated with the onset of acute NAION, and where the timing of onset can be identified by the patient.[5]

They classified the cases as definite, possible, or not NAION. The control window time prior to acute NAION onset was 30 days, and each window was 1 day in

length. The exposure status of the day prior to acute NAION onset (the case window) was compared with the exposure status of the 29 1-day periods prior to the case windows. A window was considered exposed if any part of it fell within 5 half-lives of ingestion of a PDE-5 inhibitor. Five half-lives equate to 1 day for Viagra usage and 4 days for Cialis usage.[5]

The total of 673 potential cases of acute NAION were enrolled, 81 subjects reported exposure to PDE-5 inhibitors in the 2months prior to NAION symptom onset, and 592 subjects were enrolled as unexposed. The subjects provided their information via telephone interviews. If the subjects reported PDE-5 inhibitor use during the 60days prior to onset, they completed a telephone interview with the Study Call Center. The subjects were asked to recall dates of use and the specific PDE-5 inhibitor product. Furthermore, they needed to provide their average weekly frequency of medication usage and any unusual days of usage. During the phone interviews 5 out of the 81 exposed cases were confirmed to not being exposed during the 60days prior to onset. Of the 76 subjects left, 48 were adjudicated as *definite* NAION cases, 24 were *possible* cases, and 4 were as *non-cases*. There were 43 of the 48 *definite* cases who were exposed on at least 1 day, but not all of the 30days prior to onset; these cases were used in the primary analysis.[1]

The authors found that in the *definite* NAION cases the OR were larger in the subjects <65 years (OR = 2.44), with a history of hypertension (OR = 2.41), with no history of hyperlipidemia (OR = 2.64), with no history of smoking (OR = 2.90), with no concomitant use of agents acting on the renin-angiotensin system (OR = 2.54), and with no concomitant use of aspirin (OR = 2.85). As a result this study concluded that there

was an approximately twofold increased risk of acute NAION within 5 half-lives of PDE-5 inhibitor use.[1]

Pomeranz et al (2005)

This case review article[6] was performed in 2005. The University of Minnesota reviewed the medical records of 7 patients whom developed NAION after ingestion of sildenafil (Viagra). These patients were aged between 50 and 69 years, and had typical features of NAION within 36hours of ingestion of PDE-5 inhibitors. All of the patients presented with blurred vision and loss of visual field, and in some cases the loss of visual acuity progressed over days or weeks. Furthermore, these patients had at least one arteriosclerotic risk factor (see Table 2).[6]

Pomeranz et al (2002)

This is the other case review article[7] by the same author and was performed in 2002. Five patients were identified as developing NAION after ingestion of sildenafil (Viagra) from the medical records of 4 neuro-ophthalmologists. The authors of this case review gave attention to the time of development of ocular symptoms after ingestion of medication, visual acuity, pupillary examination, as well as a follow-up examination. These medical records were retrospectively reviewed in a non-masked manner.[7]

Four of the 5 patients reported loss of vision in the affected eye within a short period of time (minutes to hours) after oral ingestion of the medication. Additionally, these 4 patients had no documented vascular risk factors; however, one case had a

previous episode of NAION. Documented visual acuity and symptoms, at presentation, were variable (see Table 2).[7]

DISCUSSION

By integrating the results from these 3 articles,[5-7] the consensus was that there is a possible linkage between the ingestion of PDE-5 inhibitors and the development of acute NAION. The observation study and case reviews, although a small sample size, showed a strong correlation between the medication and the disease progression, with the observation study [5] demonstrating a twofold increase in the risk. The patients developed visual loss within 1 to 2 days, after ingestion of the medication. These developed symptoms are damaging and permanent to the optic nerve.

In appraising the current evidence, there were a few limitations that presented during the research. One of the major concerns was in the variability across the articles. Although 25 articles appeared in the keyword search, only 1 observational study and 2 case review articles meet the inclusion criteria. Also, the small sample size provided limitations. The observational study[5] only used 43 cases and the case reviews[6,7] used a total of 12 patients. Furthermore, the observational study[5] used telephone interviews for follow-up information, instead of an actual examination. These telephone interviews relied heavily on the patient's recall of drug ingestion. Although, these articles have their limitations the evidence is brought to light and further research is necessary to provide better care for the patients.

While, the correlation between PDE-5 inhibitors and the development of NAION is lacking good quality clinical research, additional investigation on this subject can better equip clinicians when prescribing this drug class. While the research is still in its

early stages, researchers should put more into exploring side effects especially if they want to better inform patients. If the research, indeed, finds a correlation, then perhaps further research into other products with fewer side effects would gain momentum. Nevertheless, further research will enable providers to counsel and educate their patients on the more harmful and permanent side effects of PDE-5 inhibitors.

CONCLUSION

PDE-5 inhibitors are the choice of treatment for erectile dysfunction and are, very effective for treating this disease. Given the current suggestion of a link between PDE-5 inhibitor use and acute NAION though, further research is needed. There is a lack of clinical trials, which are essential in proving this correlation. Further research will allow providers to be more cognizant when prescribing this medication. Additionally, it will make patients more aware of the side effects and help them to understand when to seek help to prevent supplementary damage.

References

1. Pomeranz, HD. The Relationship Between Phosphodiesterase-5 Inhibitors and Nonarteritic Anterior Ischemic Optic Neuropathy. Journal of Neuro-Ophthalmology. 2016; 36: 193-196.
2. Cote RH. Characteristics of photoreceptor PDE (PDE6): similarities and differences to PDE5. International Journal of Impotence Res 2004; 16 (Supp 1): S28-S33.
3. Thurtell, MJ and Tomsak, RL. Nonarteritic anterior ischemic optic neuropathy with PDE-5 inhibitors for erectile dysfunction. International Journal of Impotence Research (2008) 20, 537-543.
4. Nawaaz, Nathoo, Etminan, Mahyar, and Mikelberg, Frederick. Association Between Phosphodiesterase-5 Inhibitors and Nonarteritic Anterior Ischemic Optic Neuropathy. Journal of Neuro-Ophthalmology. 2015; 35: 12-15.
5. Campbell UB, Walker AM, Gaffney M, et al. Acute nonarteritic anterior ischemic optic neuropathy and exposure to phosphodiesterase type 5 inhibitors. *J Sex Med*. 2015; 12:139-151.
6. Pomeranz HD, Smith KH, Hart WM Jr, Egan RA. Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. Ophthalmology. 2002; 109:584-587.
7. Pomeranz HD, Bhavsar, Abdhish. Nonarteritic Ischemic Optic Neuropathy Developing Soon After Use of Sildenafil (Viagra): A Report of Seven New Cases. Journal of Neuro-Ophthalmology. 2005; 25: 9-13.

Table 1. GRADE Assessment: Characteristics of Reviewed Studies

Design	*Included Outcomes*	*Downgrade Criteria*					*Quality*
		Limitations	*Indirectness*	*Imprecision*	*Inconsistency*	*Publication bias likely*	
Campbell et al (2015)							
Observational	PDE5 inhibitor ingestion, exposure period, risk of acute NAION	Serious[a]	Not serious	Serious[b]	Not serious	Unlikely	Very low
Pomeranz et al (2005)[6]							
Case Series	Pre-existing risk, exposure period	Very serious[c]	Not serious	Serious[b]	Not serious	Unlikely	Very low
Pomeranz et al (2002)[7]							
Case Series	Transient visual changes, NAION, PDE5 inhibitor ingestion	Very serious[c]	Not serious	Serious[b]	Not serious	Unlikely	Very low

[a] High risk of recall bias
[b] Small sample size
[c] Lack of control group and blinding

Table 2: Case Review Summary

Reference	Case	Age	Co-morbidity	Symptoms	Onset	Eye	Exam duration	Final Visual Acuity	Defect
Pomeranz et al (2005)[6]	1	59	ED, skin CA, HA, depression	Bright colors, vision loss	Hours	OU	1year	HM OS, LP OD	Pale optic disc OS
	2	58	ED, elevated cholesterol	Loss of vision OD	Immediate	OD	2mon	HM	Pale optic disc
	3	67	HTN, seizure	Loss of vision OD	24hours	OD	2 years	20/200	Depress VF OD
	4	50	Not mentioned	Worsen vision OS	30hours	OS	4mon	CF	Pallor optic disc
	5	69	HTN, a-fib, ED, CA (prostate)	Loss of vision OS	24hours	OS	6mon	20/125	Pale optic disc
	6	66	DM, HTN, elevated cholesterol	Loss of vision OD	36hours	OD	30mon	20/30	Pale optic disc
	7	60	Elevated cholesterol	Shade coming down	Next AM	OD	3mon	20/20	Pallor ON
Pomeranz et al (2002)[7]	1	52	Prostate CA, Crohn's	Blurry vision	1hour	OS	9mon	20/20	Pallor ON
	2	69	Elevated cholesterol	Painless vision loss	45mins	OD	3wks	20/80	Pallor ON
	3	42	None	Blurry vision	12hours	OD	2mon	20/200	Pale ON
	4	62	NAION in 1997	Decrease vision	Unclear	OD	3mon	20/50	Pallor ON
	5	59	DM, CAD		Several hours	OD	1wk	20/25	Inferior VF defect

KEY: ON (optic nerve), CA (cancer), OU (both eyes), OS (left eye), OD (right eye), DM (diabetes mellitus), CAD (coronary artery disease), VF (visual field), HA (headache), HM (hand motion), LP (light perception), HTN (hypertension), CF (count fingers)